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REVIEW

Renal sympathetic denervation for treatment of ventricular arrhythmias: a review on current experimental and clinical findings

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Abstract Ventricular arrhythmias (VAs) remain the major cause of mortality and sudden cardiac death (SCD) in almost all forms of heart disease. Despite so many therapeutic advances, such as pharmacological therapies, catheter ablation, and arrhythmia surgery, management of VAs remains a great challenge for cardiologists. Evidence from histological studies and from direct nerve activity recordings have suggested that increased sympathetic nerve density and activity contribute to the generation of VAs and SCD. It is well known that renal sympathetic nerve (RSN), either afferent component or efferent component, plays an important role in modulation of central sympathetic activity. We have recently shown that RSN activation by electrical stimulation significantly increases cardiac and systemic sympathetic activity and promotes the incidence of acute ischemia-induced VAs, suggesting RSN has a role in the development of VAs. Initial experience of RSN denervation (RDN) in patients with resistant hypertension showed that this novel and minimally invasive device-based approach significantly reduced not only kidney but also whole-body norepinephrine spillover. In addition, experimental studies find that left stellate ganglion nerve activity is significantly decreased after RDN. Based on these observations, it is reasonable to conclude that RDN may be an effective therapy for the management of VAs. Indeed, RDN has provided a protection against VAs in both animal models and patients. In this article, we review the role of the RSN in the generation of VAs and SCD and the role of RDN as a potential treatment strategy for VAs and SCD.

Keywords Autonomic nervous system · Renal sympathetic denervation · Ventricular arrhythmias · Sudden cardiac death · Ventricular tachycardia storm

Abbreviations

APD	Action potential duration
ERP	Effective refractory period
LSG	Left stellate ganglion
RDN	Renal sympathetic denervation
RSN	Renal sympathetic nerve
SCD	Sudden cardiac death
VAs	Ventricular arrhythmias
VT	Ventricular tachycardia

Introduction

Ventricular arrhythmias (VAs) remain the major cause of mortality and sudden cardiac death (SCD) in almost all forms of heart disease [1, 2]. Although pharmacological therapies have an important role in the reduction of symptomatic VAs, side-effects and therapeutic failures happen in some patients [3]. For drug-refractory symptomatic patients, catheter ablation is important for reducing the frequency of VAs, especially in patients with idiopathic arrhythmias and without structural heart disease [3, 4]. However, in some cases, these therapeutic strategies may not suffice to suppress the incidence of VAs. Inhibition of

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sympathetic activity might be an effective choice in these particular cases, since an increase in sympathetic activity contributes to the genesis of VAs [5]. For example, left cardiac sympathetic blockade has been considered in patients with drug or ablation-refractory VAs [6, 7].

Catheter-based renal sympathetic denervation (RDN), a new approach to decrease sympathetic activity, was firstly reported by Krum et al. [8] in 2009 in patients with refractory hypertension. Over the past 4–5 years, this novel and minimally invasive device-based approach has shown promising therapeutic effects for several clinical conditions associated with chronic sympathetic activation, besides refractory hypertension [9–11]. Other collateral benefits have been reported for heart failure [12, 13], chronic kidney disease [14], obstructive sleep apnea [15], impaired glucose metabolism [15, 16], and atrial fibrillation [17–20]. Recently, several basic studies [21–23] and clinical case reports [24–30] have suggested that RDN is also an effective and safe approach for the treatment of ischemic or non-ischemic VAs. In this article, we review such novel device-based approach as a potential treatment strategy for VAs.

Role of sympathetic nervous system in the genesis of VAs and SCD

It is well accepted that the autonomic nervous system has an important role in the genesis and maintenance of VAs and SCD. Thus, modulating autonomic tone, especially inhibition of sympathetic tone, has been proposed as a method to the treatment of VAs and SCD [5, 31].

In a histological study with explanted hearts, Cao and colleagues [32] found that patients who had a history of VAs/SCD had increased density of sympathetic nerves compared to patients with similar structural heart disease but no arrhythmias, indicating that abnormally increased sympathetic nerve sprouting is in part responsible for the occurrence of VAs and SCD. Subsequently, Chen et al. [33] showed that infusion of nerve growth factor or applying sub-threshold electrical stimulation [34] to the left stellate ganglion (LSG) in dogs with myocardial infarction could increase sympathetic nerve sprouting and facilitate ventricular fibrillation and SCD, further suggesting a causal relationship. In rabbits fed with high cholesterol, there was a significant increase in nerve sprouting, sympathetic innervation, as well as ventricular vulnerability to fibrillation [35]. With directly recording nerve activity from the LSG in a canine model of SCD, Zhou et al. [36] found that increased sympathetic nerve discharges were the major triggers for malignant VAs. In addition, a series of studies in isolated rabbit hearts by Ng et al. [37, 38] showed that sympathetic nerve stimulation could increase maximum slope of restitution but decrease ventricular effective refractory period (ERP), action potential duration (APD), and ventricular fibrillation threshold. These findings suggest that increased sympathetic activity and associated ventricular electrophysiological remodeling have an important role in the generation of VAs and SCD (Fig. 1).

Considering the evidence involving autonomic mechanisms, antiadrenergic therapies should provide effective protection against VAs and SCD. Beta-blockers have been shown to reduce the incidence of ventricular tachyarrhythmias, particularly in the setting of cardiac ischemia [39, 40]. Left cardiac sympathetic denervation, e.g., LSG resection, reduced VAs in high-risk patients and dogs following myocardial infarction [41, 42] and in patients with inherited arrhythmia syndromes [43–45]. Spinal cord stimulation, which shows anti-sympathetic effects, improves cardiac function and decreases VAs in a canine model of post-infarction heart failure [46]. High thoracic epidural anesthesia, which reduces sympathetic traffic to the heart, can prevent VAs during acute myocardial ischemia in rats [47]. Our recent study showed that carotid baroreceptor stimulation displayed a beneficial effect on acute ischemia-induced VAs by sympathetic withdrawal [48]. Therefore, inhibition of sympathetic activity is a promising therapy for VAs and SCD.

Role of kidney in modulation of sympathetic activity and in the generation of VAs

The kidney communicates with the central sympathetic nervous system via renal sympathetic nerves (RSNs), which consist of efferent and afferent fibers. These nerves follow the renal artery to the kidney and are found primarily in the adventitia of the renal arteries [49]. Activation of renal efferent nerves results in volume retention, a reduction in renal blood flow, and activation of renin-angiotensin-aldosterone system through renin release [50]. Renal ischemia, hypoxia, oxidative stress, and other triggers can activate renal afferent nerves, directly influencing sympathetic outflow from the brain stem to the kidneys and other highly innervated organs [50]. Chinushi et al. [51] showed that electrical stimulation of RSN could increase the systemic blood pressure, serum catecholamine, and sympathetic nerve indices of heart rate variability, suggesting an increase in systemic sympathetic nervous activity.

In addition to modulation of the systemic sympathetic activity, we have recently shown that activation of RSN by 3-h electrical stimulation is also able to increase LSG nerve activity and promote the incidence of acute ischemia-induced VAs which can be attenuated by LSG ablation [52], indicating that there is a connection between RSN and

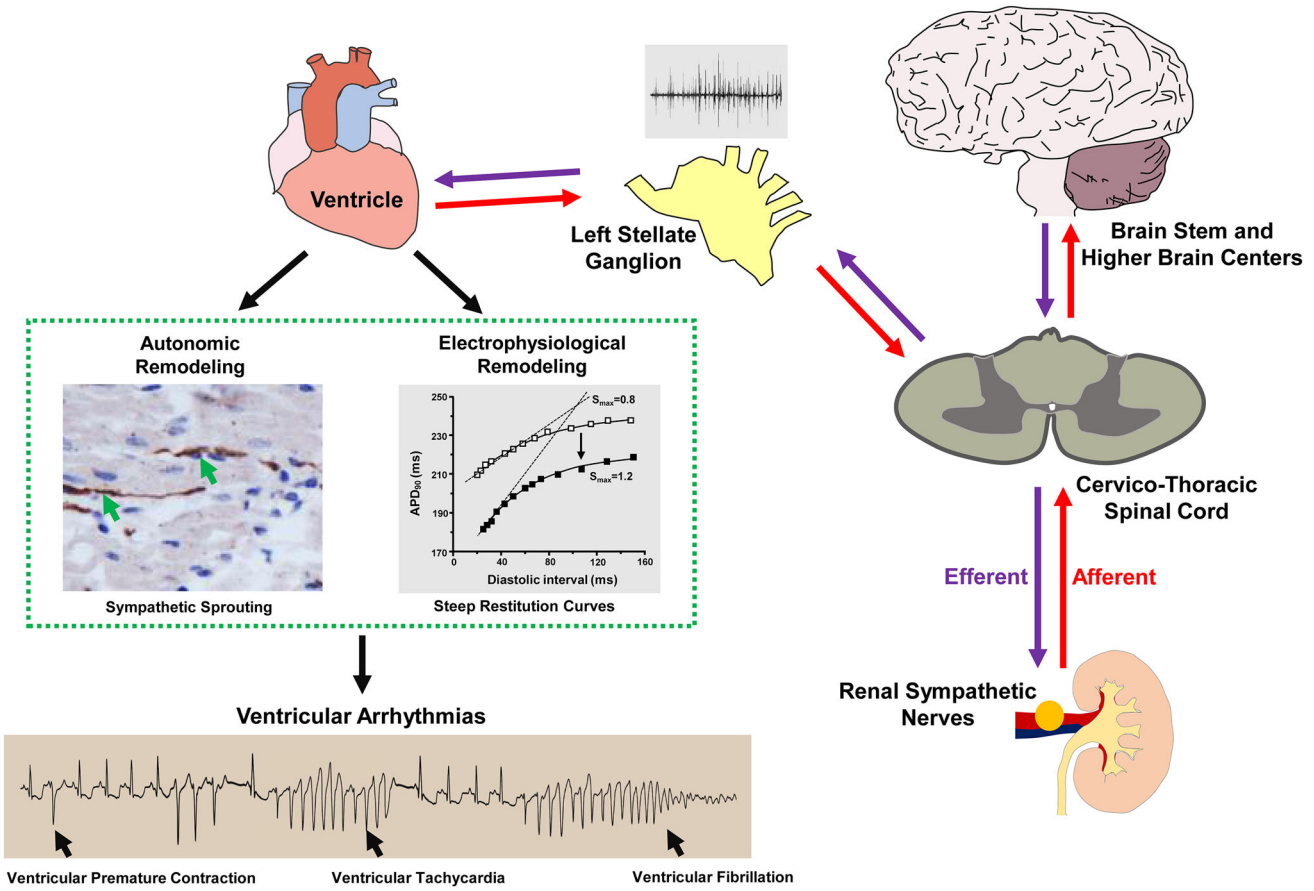

Fig. 1 Cardio-renal neuraxial pathways of sympathetic nerve signaling. Renal sympathetic activation can increase nerve activity of left stellate ganglion (LSG) by increasing central sympathetic output, inducing sympathetic nerve sprouting and electrophysiological remodeling in the ventricle, which are important triggers for ventricular arrhythmias (VAs). In contrast, renal sympathetic denervation is able to decrease the whole-body sympathetic activity as well as the nerva activity of LSG, which may offer a protective effect on VAs

LSG [53] (Fig. 1). Clinically, compared with patients with normal renal function, patients with chronic kidney disease have a higher risk for SCD [54, 55]. Taken together with the demonstration that the kidney plays an important role in modulation of both systemic and cardiac sympathetic activity, and RSN appears to be involved in the pathogenesis of VAs and SCD [56] (Fig. 1).

RDN as a novel approach to decrease sympathetic activity

A recent clinical study (Symplicity HTN-3) showed the absence of beneficial effects with RDN in comparison to the sham procedure in terms of blood pressure reduction [57]; however, these results might be partially due to increased placebo effect, operator learning curve, procedural discrepancies, and lack of a "biomarker" for ablation endpoint. Recently, considerable publications [58–60] still continuously reported the efficacy of RDN for the improvement of blood pressure in patients with resistant hypertension. Besides, RDN also showed therapeutic effects in other conditions due to an excessive hyper-sympathetic condition, such as heart failure [12], chronic kidney disease [14], obstructive sleep apnea [15], and impaired glucose metabolism [15, 16]. In resistant hypertension patients, RDN has been found to reduce renal norepinephrine spillover by 48 % [8], as well as muscle sympathetic nerve activity by 37 % [61]. Basic and clinical studies have both shown that RDN is able to reduce the heart rate and AV-conduction velocity, suggesting that RDN may be associated with an antiadrenergic effect [62, 63]. In ambulatory dogs, Tsai et al. [64] recorded LSG nerve activity before and after RDN using implanted radiotransmitters. They found that the 24-h average LSG nerve activity decreased from 275 mV-s at baseline to 233 mV-s 4 weeks after RDN. In a hyper-sympathetic atrial fibrillation model, Hou et al. [65] showed that LSG stimulation plus rapid atrial pacing induced an elevation in blood pressure, an increase in the sympathetic indices of

heart rate variability, and a rise in plasma norepinephrine level, which could be reversed by the catheter-based RDN. These observations indicate that sympathetic denervation from kidney is able to reduce not only systemic but also cardiac sympathetic activity, therefore, may be a promising therapy for VAs and SCD.

Basic evidence for the treatment of VAs by RDN

In a recent study conducted by Linz and colleagues [21], anesthetized pigs were subjected to 20 min of acute left ventricular ischemia followed by reperfusion. They found that these pigs that underwent RDN treatment were associated with lower occurrence of VAs during ischemia compared to those that underwent sham RDN. However, RDN did not affect reperfusion-induced arrhythmias. A very recent study from our group similarly showed that RDN significantly decreased the episodes of VAs during 1-h of acute myocardial ischemia [22]. In this study, we also investigated the effects of RDN on ventricular electrophysiological properties in normal canine heart. We found that RDN significantly prolonged ventricular effective refractory period (ERP) and action potential duration (APD), reduced the dispersion of ERP and the slope of the restitution curve, and suppressed APD alternans, suggesting that RDN was able to stabilize ventricular electrophysiological properties in normal hearts. In a canine model of pacing-induced heart failure, Guo et al. [23] showed that RDN significantly decreased the corrected QT interval, the dispersions of QT interval and ventricular ERP, the heterogeneity of Cx43 distribution in ventricle, as well as the ventricular fibrillation inducibility. Their results suggested that attenuating the ventricular substrate and electrophysiological remodeling may be the potential mechanisms underlying the favorable effects of RDN on VAs in the pacing-induced heart failure model. These studies provided basic evidence that RDN was an effective therapy for the treatment of VAs associated with acute myocardial ischemia or chronic pacing-induced heart failure.

Initial clinical experience with RDN in the management of ventricular tachycardia (VT) storm

There are six small studies [24–29], so far, enrolling only 11 patients (10 males) and initially assessing the feasibility, potential efficacy, and safety of RDN in patients with resistant VT storm (Table 1).

Ukena et al. [24] reported the first-in-man experience of RDN for the treatment of VT storm in 2 patients with chronic heart failure (NYHA III). The first patient had hypertrophic cardiomyopathy, suffering from recurrent monomorphic VT despite multiple antiarrhythmic attempts, including repeated endocardial and epicardial electrophysiological ablations. The second patient, with dilated non-ischemic cardiomyopathy, had recurrent polymorphic VT and ventricular fibrillation but refused catheter ablation. After obtaining informed patient consent, both the patients underwent a bilateral RDN with six ablations at 8 W for 2 min each, without any apparent procedural complications. Blood pressure remained stable during the procedure and follow-up. In both the patients, ventricular tachyarrhythmias were significantly reduced in the first few days after RDN and finally dissipated during up to 6-month follow-up. Interestingly, the second patient who began to use insulin medication 4 years before RDN was able to continuously reduce and eventually terminate this medication.

Clinically using RDN in the treatment of acute myocardial infarction-related VT storm was first reported by Hoffmann et al. [25]. In this case report, a 63-year-old patient who successfully underwent thrombus extraction and percutaneous coronary intervention continued to show recurrent monomorphic VT and fibrillation episodes despite maximum dose of antiarrhythmic drug therapy. VT ablation still failed to eliminate the episodes of ventricular tachyarrhythmias. Due to an increasing instability, RDN was performed. The frequency of episodes dramatically decreased from 3.2/day pre-ablation (6 days, 19 episodes) to 1.8/day post-ablation (6 days, 11 episodes), and the patient had no further VAs episodes after day 23 and up to 6-month follow-up.

Recently, Remo et al. [27] reported four patients with cardiomyopathy (2 non-ischemic, 2 ischemic) suffering from recurrent monomorphic or polymorphic VT despite maximized antiarrhythmic therapy and prior ablation. RDN was successfully performed without any acute or chronic complications. The number of VT episodes was decreased from 11.0 ± 4.2 during the month pre-ablation to 0.3 ± 0.1 per month post-ablation. Another new finding of this study was that the responses to RDN were similar for ischemic and non-ischemic patients.

Similar conclusions were reached by Staico et al. [26] and Scholz et al. [28], who also showed that RDN was effective and safe for the treatment of resistant VT storm in dilated cardiomyopathy patients. Although single-sided RDN in patients with renal artery stenosis was questioned by Wang [66], several case reports suggest that single-sided RDN may be effective and safe in selected patients [67, 68]. Interestingly, Hilbert et al. [29] recently reported that single-sided RDN was able to prevent the episodes of VTs as well in a patient with ischemic cardiomyopathy. These case reports described above only evaluated the implication of RDN in old people (age range 57–83 years). A recent case report by Kosiuk et al. [30] has demonstrated

Table 1 Characteristics of patients included in the case reports

References	Age (gender)	Cardiomyopathy (LVEF)	Baseline arrhythmias	Prior treatment attempts	Follow-up (months)	Post-RDN arrhythmias
Ukena et al. [24]	67 (male)	Non-obstructive hypertrophic (40 %)	Multiple, monomorphic VT	Endo- and epicardial ablation; betablocker, amiodarone, mexiletine, lidocaine	6	One episode at 4th week; no further episodes
	57 (male)	Idiopathic dilated (28 %)	Multiple, polymorphic VT or VF	Amiodarone; declined ablation	6	12 episodes within first 24 h; no further episodes
Hoffmann et al. [25]	63 (male)	Acute ischemic (seriously impaired)	Multiple, monomorphic VT	Endocardial ablation; amiodarone	6	Six episodes within the 1st month; no further episodes
Staico et al. [26]	62 (male)	Dilated (unclear)	Multiple VT	Amiodarone, lidocaine, betablocker; ablation is contraindicated	5	11 episodes within the 1st month; no further episodes
Remo et al. [27]	68 (male)	Non-obstructive (45–50 %)	Multiple slow VT	Endocardial ablation × 2; amiodarone, lidocaine, procainamide, esmolol	10	Two episodes within the 1st months; no further episodes
	83 (male)	Non-ischemic (30–35 %)	Monomorphic VT	Endocardial ablation; sotalol	9	Two episodes each at 2nd and 4th month; no further episodes
	63 (female)	Ischemic (30 %)	Monomorphic VT	Endo- and epicardial ablation; amiodarone	11	Four episodes at 3.5 month; no further episodes
	60 (male)	Ischemic (15–20 %)	Multiple, monomorphic VT	Endocardial ablation; amiodarone, metoprolol	5	Two episodes within the 1st month; no further episodes
Scholz et al. [28]	57 (male)	Dilated (25 %)	Multiple, monomorphic VT	Endo- and epicardial ablation; dry epicardial puncture; amiodarone, carvedilol	5	One episode at 2nd month; no further episodes
Hilbert et al. [29]	60 (male)	Ischemic (21 %)	Multiple VT	Endo- and epicardial ablation; amiodarone, metoprolol	12	Two more episodes within the 1st week; no further episodes after another VT ablation
Kosiuk et al. [30]	23 (male)	Ischemic (45 %)	Multiple, monomorphic VT	Endo- and epicardial ablation; sotalol	10	No episodes

Table 2 Overview of design, sites, and time schedule of ongoing trials

Trial identifier	Official title	Sites	Interventions	Status	Expected completion date
NCT01858194	Renal sympathetic denervation as an a adjunct to catheter-based VT ablation	Mount Sinai School of Medicine, New York, New York, US	VT ablation vs VT ablation + RDN	Recruiting	11/2016
NCT02071511	Renal denervation in patient undergoing VT ablation: combined renal denervation and VT ablation vs. simply VT ablation	Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany	VT ablation vs VT ablation + RDN	Recruiting	04/2018

that young people with therapy-resistant VT storm also can be treated by RDN. A 23-year-old male patient with ischemic cardiomyopathy suffered from VT storm despite both endocardial and epicardial catheter ablations, and maximum tolerable dose of beta-blockers. No evidence of VT which allowed reduction of antiarrhythmic drug dosage was achieved 3 days after the performance of RDN and during 10 months of follow-up.

Present challenges and future directions

Although this novel therapeutic approach appears promising in the treatment of VAs, only 11 patients with therapy-resistant VT storm were enrolled in these cases. Therefore, it warrants further clinical investigation. Accordingly, two ongoing trials (NCT01858194 and NCT02071511, Table 2) will provide a more precise definition of the role of RDN in the treatment of VAs.

For this novel technology, there are several challenges with RDN, not only in patients with resistant hypertension but also in patients with VAs. The first challenge is the selection of patients. Genesis of VAs is multifactorial, including not only sympathetic activation but also genetic factor, electrolyte disorder, and organic heart disease. Therefore, simply stating that a patient with VAs will be assigned to RDN therapy is inexact. Since RDN has shown to reduce efferent renal and central sympathetic activity [10], it is likely that patients with pronounced sympathetic overactivity would benefit the most from RDN [69]. Assessment of sympathetic activity before RDN may be suggested to perform in future studies. The second challenge being equally important is the selection of ablation parameters, including power, temperature, ablation time, impedance, and number of ablations. To date, several RDN systems have been employed in clinical studies, such as Medtronic's Symplicity system, St. Jude's Enlig HTN system, Vessix's V2 system, and so on [70]. It should be noted that these systems displayed different ablation parameters which were chosen on the basis of limited animal and human autopsy data. None of the settings have been confirmed by pre-clinical studies. Therefore, future studies should meticulously investigate the effectiveness of ablation with different procedural parameters. Another possible reason for the incomplete ablation is lack of effective method to identify the ablation target and confirm the endpoint of ablation, and this is the third challenge. Electrical stimulation of renal arteries before and after ablation has been proposed as a method to identify renal nerves and confirm the completeness of RDN both in animals [22, 51, 71] and in patients [17, 72]. However, this method was questioned by Tsiachris et al. [73], who suggested that renal hemodynamic parameters may be used as direct invasive markers of successful of RDN [74]. Anyway, the best method of identification of renal nerves and confirmation of complete ablation also need further study to explore.

Conclusions

VAs remain the major cause of mortality and SCD in almost all forms of heart disease. Despite so many therapeutic advances, such as pharmacological therapies, catheter ablation, and arrhythmia surgery, management of VAs remains a great challenge for cardiologists. Increased sympathetic activity is important in the generation of VAs and SCD. The kidney has been shown to play an important role in modulation of both systemic and cardiac sympathetic activity. Basic and clinical studies recently suggest that RDN is able to reduce not only systemic but also cardiac sympathetic activity, indicating that RDN may be a promising therapy for VAs and SCD. Indeed, RDN has provided a protection against VAs in both animal models and patients. However, all the initial clinical data so far are case reports without satisfactory trial design, and publication bias cannot be excluded. The ongoing trials will provide a more precise definition of the role of RDN in the treatment of VAs. However, since this is a novel therapy strategy, several challenges (e.g., selection of patients and ablation parameters) need to be addressed before being widely used.

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Conflict of interest None.

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